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ORIGINAL RESEARCH

Duration of Inducible Ventricular Tachycardia Early After ST-Segment–Elevation Myocardial Infarction and Its Impact on Mortality and Ventricular Tachycardia Recurrence

Tejas Deshmukh, MBBS, MClinTRes; Sarah Zaman, MBBS, PhD; Arun Narayan, BNurs, MNurs (Critical Care); Pramesh Kovoor, MBBS, PhD

BACKGROUND: The clinical significance of the duration of inducible ventricular tachycardia (VT) at electrophysiology study (EPS) in patients soon after ST-segment–elevation myocardial infarction and its predictive utility for VT recurrence are not known.

METHODS AND RESULTS: Consecutive ST-segment–elevation myocardial infarction patients with day 3 to 5 left ventricular ejection fraction ≤40% underwent EPS. A positive EPS was defined as sustained monomorphic VT with cycle length ≥200 ms. The induced VT was terminated by overdrive pacing or direct current shock at 30 s or earlier if hemodynamic decompensation occurred. Patients with inducible VT duration 2 to 10 s were compared with patients with inducible VT >10 s. The primary end point was survival free of VT or cardiac mortality. From 384 consecutive ST-segment–elevation myocardial infarction patients who underwent EPS, 29% had inducible VT (n=112, 87% men). After mean follow-up of 5.9±3.9 years, primary end point occurred in 35% of patients with induced VT 2 to 10 s duration (n=68) and in 22% of patients with induced VT >10 s (n=41) (*P*=0.61). This was significantly different from the noninducible VT group, in which primary end point occurred in 3% of patients (n=272) (*P*=0.001).

CONCLUSIONS: This study is the first to show that in patients who undergo EPS early after myocardial infarction, inducible VT of short duration (2–10 s) has similar predictive utility for ventricular tachyarrhythmia as longer duration (>10 s) inducible VT, which was significantly different to those without inducible VT. It is possible that immediate cardioversion of rapid VT might have contributed to some of the short durations of inducible VT.

Key Words: electrophysiology study ■ myocardial infarction ■ ventricular tachycardia

Electrophysiology study (EPS) demonstrates the presence of an electrical substrate for reentrant ventricular tachyarrhythmia. The inducibility of ventricular tachycardia (VT) at EPS is predictive of spontaneous ventricular arrhythmias late after myocardial infarction (MI) in patients with impaired ventricular function.[1–5] EPS has been used as a risk stratification tool to guide prophylactic implantable cardiac defibrillator (ICD) implantation in observational and randomized defibrillator trials.[6,7]

The aim of the present study was to assess the impact of the duration of inducible VT at the index EPS on the primary end point of survival free of VT or cardiac mortality.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. Consecutive patients (n=384) with

Correspondence to: Pramesh Kovoor, MBBS, PhD, Department of Cardiology, Westmead Hospital, Corner Darcy and Hawkesbury Roads, Westmead, New South Wales, Australia 2145. E-mail: pramesh.kovoor@sydney.edu.au

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CLINICAL PERSPECTIVE

What Is New?

- Inducible ventricular tachycardia (VT) that was both short and of longer duration (>10 s) had similar predictive value for the combined end point of mortality or VT recurrence, which was significantly different to those without inducible VT.

What Are the Clinical Implications?

- We propose the following new definitions for inducible VT at early electrophysiology study after acute myocardial infarction.
- Sustained VT should be defined as >8 beats and >2 s.
- Nonsustained VT should be defined as <8 beats and <2 s duration.

Nonstandard Abbreviations and Acronyms

ATP	antitachycardia pacing
CL	cycle length
EPS	electrophysiology study
ICD	implantable cardiac defibrillator
LVEF	left ventricular ejection fraction
MI	myocardial infarction
PCI	percutaneous coronary intervention
PVS	programmed ventricular stimulation
STEMI	ST-segment–elevation myocardial infarction
VF	ventricular fibrillation
VT	ventricular tachycardia

ST-segment–elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) from 2004 to 2017, who had an early EPS after STEMI, were prospectively recruited. The study was approved by the Western Sydney Local Health District Human Research Ethics Committee, and all patients gave their informed consent. Patients either presented directly to the intervention-capable tertiary referral Westmead Hospital or were referred by 3 associated district hospitals. All patients in the study were taken to the cardiac catheterization laboratory with angiographically confirmed STEMI and intention for primary PCI. No patients received thrombolytic therapy. Patients underwent inpatient assessment of left ventricular ejection fraction (LVEF) at day 3 to 5 with gated heart pool scan, transthoracic/transesophageal echocardiogram, or sestamibi scan. All patients were commenced on optimal medical therapy, including β blockers, angiotensin-converting enzyme inhibitor, statins, and dual antiplatelet medications. Patients with LVEF ≤40% underwent inpatient EPS to determine need for an early post-MI primary prevention ICD.

Electrophysiology Study

EPS was performed under conscious sedation in the absence of antiarrhythmic medication. β Blockers apart from sotalol were not withheld. Patients were closely monitored during EPS with constant pulse oximetry recording, noninvasive blood pressure, and end tidal CO_2 recording in addition to cardiac rhythm monitoring. Programmed ventricular stimulation (PVS) was performed at twice diastolic threshold at the right ventricular apex (single site) using a programmable stimulator.[5] A drive train (S1) of 8 beats at 400 ms was followed by up to 4 extrastimuli.[8] Stimuli were rectangular pulses of 2-ms duration at twice diastolic threshold with a 3-s delay between each drive train. The initial extrastimulus was delivered at a coupling interval of 300 ms and then decreased in 10-ms steps to ventricular refractoriness. If the earliest possible extrastimulus (eg, S1S2) failed to induce VT, that extrastimulus was delivered 10 ms outside the ventricular effective refractory period and an additional extrastimulus was added (eg, S2S3) at a coupling interval of 300 ms. The additional extrastimulus was decreased in 10-ms steps in the same manner. Additional extrastimuli were added in a similar manner (always starting with a coupling interval of 300 ms) until VT, ventricular fibrillation (VF), or ventricular flutter (<200-ms cycle length [CL]) was induced or refractoriness of the fourth extrastimulus (S5) was reached. There was no set lower limit for the shortest permissible extrastimulus coupling interval. Isoprenaline infusion was not used to facilitate VT induction. A positive EPS was defined as sustained monomorphic VT CL ≥200 ms[9,10] for >10 s or shorter duration if hemodynamic compromise occurred. Loss of pulse oximeter tracing was a sensitive indicator of hemodynamic instability, necessitating termination of the induced VT. Our electrophysiology laboratory protocol requires a nurse dedicated to defibrillation during PVS who charges the device to a prespecified value at the onset of the tachyarrhythmia, enabling rapid defibrillation in cases of hemodynamic instability during induced VT. This avoided delays and failure of defibrillation. The inducible VT terminated spontaneously or required therapy in the form of antitachycardia pacing (ATP) or direct current shock. A negative EPS was defined as no arrhythmia induced or inducible VF/ventricular flutter CL <200 ms. If the first PVS protocol using up to 4 extrastimuli was positive for inducible VT, the study

was stopped and further PVS inductions were not performed. If the first PVS was negative, a repeated PVS[11] was performed from the same site after a period of 5 to 10 minutes, using the same protocol of up to 4 extrastimuli. If the second PVS failed to induce VT, this would be classified as a negative EPS. Predischarge ICD implantation was recommended for patients with inducible VT at EPS.[4,6,9]

Patients were divided into 2 groups based on the duration of inducible VT of 2 to 10 and >10 s.

ICD Implantation and Programming

All devices were prepectoral or subpectoral systems with the manufacturer and type determined by the hospital device acquisition process. Defibrillator threshold testing was not part of study protocol but was performed at the time of implantation at the discretion of the proceduralist. Device detection and therapy were programmed according to manufacturer's recommendations. Therapy for VF was ATP during charging and shock. Therapy for VT consisted of ATP followed by shock, if required.

Whenever possible, 3 detection zones were set: VF zone of CL <250 ms programmed to deliver therapy via shock; fast VT zone within the VF zone of CL 200 to 250 ms programmed to deliver ATP followed by tiered shock; and VT zone of CL 251 to 360 ms programmed to deliver ATP followed by tiered intensity shock. If 3 detection zones could not be set, VF zone of CL <250 ms and VT zone of CL 251 to 350 ms were set.

Parameters for VT/VF detection were standardized according to the ICD manufacturer. In general, for Medtronic ICDs, detection of VT CL <250 ms required 18/24 beats and subsequently 12/16 beats for redetection; for VT CL >250 ms, detection required 16 beats and subsequently 12 beats for redetection. For Boston Scientific/Guidant devices, ventricular tachyarrhythmia detection was in accordance to the "sliding window principle," with 8/10 intervals for commencement of window detection and 6/10 for continuation. For VT <240 ms, the duration timer was 1 s, with redetection for 1 s. For VT >240 ms, the duration timer was 2.5 s, with redetection for 1 s. For St. Jude devices, detection of ventricular tachyarrhythmia was based on the binning system of current interval and running interval average. VT detection required 12 binned intervals at a rate >250 ms, and VF required 12 binned intervals at a rate <250 ms.

Ventricular arrhythmia that did not reach the set number of detection intervals was classified as nonsustained and did not meet the primary end point. Discriminators for supraventricular tachycardia were standardized on the basis of arrhythmia onset, stability, QRS morphological characteristics, and ventriculoatrial dissociation.

End Points and Follow-Up

The primary end point was survival free of VT or cardiac mortality. All patients were followed up by the study investigators throughout their time in hospital and by telephone contact at 1, 3, and 6 months after discharge, with 6-monthly intervals thereafter for at least 2 years. Long-term follow-up data were obtained from electronic medical records and outpatient cardiologist reviews. Patients with an ICD were also followed up in the ICD clinic, on home monitoring, and with OneView. OneView is a web-accessible application from ScottCare (Cleveland, OH). It gives the ability to monitor and manage patients with implantable cardiac devices, regardless of the manufacturer. It is able to consolidate data from the programmer at implant or in-clinic interrogation, and from manufacturer web portals for remote device interrogations.

Ventricular tachyarrhythmia in ICD recipients included only VT that required treatment to terminate (ATP or shock). Ventricular tachyarrhythmia in non-ICD recipients included only ECG-documented sustained VT for a duration of >1 minute. Cause of death was adjudicated by 2 local investigators on the basis of information obtained from witnesses, family members, death certificates provided by the state registry of births and deaths, hospital medical records, rhythm strips, and autopsy reports. A third independent investigator adjudicated if opinion differed. The adjudicators of the primary end point were blinded to the duration of the induced VT.

Statistical Analysis

SPSS (release 24.0) was used to analyze the results. Two-tailed tests with a significance level of 5% were used throughout. The χ^2 or Fisher's exact tests, as appropriate, were used to test for association between categorical variables. ANOVA or Kruskal-Wallis equivalent was used to test for differences in the distribution of continuous variables between the groups. Survival curves were estimated using the Kaplan-Meier method and compared statistically using the log-rank test.

RESULTS

The data that support the findings of this study are available from the corresponding author on reasonable request. Baseline characteristics are shown in Table 1. The mean age was 58.6 years, with most patients being men. The mean follow-up was 5.4 years. The mean LVEF was 31%, with most patients having an occlusion in the left anterior descending artery as the culprit vessel. A total of 112 patients had a positive EPS, whereas 272 patients had a negative EPS, of whom 139 had inducible VF or flutter (CL <200 ms) and the

Table 1. Baseline Characteristics

Variable	EPS Positive (VT 2–10 s) (n=68)	EPS Positive (VT >10 s) (n=41)	EPS Negative (n=272)	*P* Value
Age, mean±SD, y	56.6±10.9	61.6±11.1	57.5+11.6	0.041
Sex (men/women)	63:5	34:7	220:52	0.073
Follow-up, mean±SD, y	7.1±3.9	4.3±2.9	4.9+3.9	0.001
LVEF, mean±SD, %	30±7	30±8	33+7	0.012
Previous CAD, %	32	18	22	0.176
Previous PCI, %	20	15	11	0.175
Previous CABG, %	5	5	1	0.091
Previous CVA, %	3	0	3	0.511
Hypercholesteremia, %	66	50	50	0.061
Diabetes mellitus, %	29	39	22	0.021
Hypertension, %	55	58	44	0.313
Smoker, past or current, %	71	71	68	0.956
Discharge ACE-I or ARB, %	81	83	82	0.952
Discharge β blocker, %	82	93	89	0.225
Discharge amiodarone, %	6	0	3	0.219
Discharge diuretics, %	30	43	11	0.001
Infarct-related artery, %				0.015
LAD	77	72	84	
RCA	11	3	8	
LCx	8	3	5	

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVA, cerebrovascular accident; EPS, electrophysiology study; LAD, left anterior descending artery; LCx, left circumflex artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RCA, right coronary artery; and VT, ventricular tachycardia.

remaining 133 had no inducible arrhythmia. There was no significant difference between the 3 groups in terms of β blocker or amiodarone prescription on discharge

Of the negative EPS patients, 4 had ICD implanted, with 2 being for reduced LVEF remote to their STEMI and 2 having episodes of sustained VT. Of the positive EPS patients, all patients went on to have an ICD implanted. Data on duration of inducible VT were not available for 3 patients, and they were excluded from the primary end point analysis. Follow-up data on VT recurrence were not available for 6 patients. EPS-positive patients had a mean CL of 230 ms and median duration of induced VT in the 2 to 10 and >10 s groups of 4 and 20 s, respectively (Table 2). Mortality and VT recurrence were not different between EPS-positive subgroups and were greater in EPS-positive patients than in EPS-negative patients (Table 3), both for survival free from VT or cardiac mortality (Figure 1) and from VT or all-cause mortality (Figure 2).

Table 2. Characteristics of EPS-Positive Patients

Characteristic	Duration of Induced VT, s		*P* Value
	2–10	>10	
Total No.	68	41	…
Cycle length, mean±SD, ms	231±35	228±22	0.732
Induced VT, median (LQ, UQ), beats/min	273 (245, 286)	273 (248, 286)	0.732
Duration of induced VT, median (LQ, UQ), s	4 (3, 6)	20 (16, 26)	0.001
Beats before termination, median (LQ, UQ)	19 (11, 25)	81 (68, 110)	0.001
Mode of termination, %			
ATP	30	37	0.008
DC shock	70	51	
Spontaneous	0	12	

ATP indicates antitachycardia pacing; DC, direct current; EPS, electrophysiology study; LQ, lower quartile; UQ, upper quartile; and VT, ventricular tachycardia.

DISCUSSION

This study is the first to show that VT recurrence and cardiac mortality were similar in patients with induced VT and hemodynamic instability (and thereby interrupted) lasting 2 to 10 s, compared with induced VT that lasted >10 s with maintained hemodynamic stability and sometimes spontaneous conversion to normal sinus rhythm, when compared with those without inducible VT. There was, however, a difference in

Table 3. Mortality Data and VT Recurrence

Variable	Duration of VT, s		EPS Negative	*P* Value
	2–10	>10		
All-cause mortality, %	12	12	6	0.206
All-cause mortality+VT recurrence, %	43	29	6	0.001
Cardiac mortality, %	3	5	2	0.677
Cardiac mortality+VT recurrence, %	35	22	3	0.001
VT recurrence, %	37	18	1	0.001

EPS indicates electrophysiology study; and VT, ventricular tachycardia.

VT recurrence between the 2 to 10 and >10 s of induced VT groups (37% versus 18%).

Most studies have defined inducible VT at the time of EPS as VT with a duration of >30 s or shorter in the event of hemodynamic compromise.[3,12–14] However, outside of EPS, nonsustained VT has been defined as anything from ≥3 consecutive ventricular beats with a rate >100 beats per minute and durations of 15 to 30 s.[15–17] The definitions of inducible VT at EPS and spontaneous VT outside of the electrophysiology laboratory are not universal. Our study demonstrates that even shorter episodes of induced VT at EPS confer a significant risk for future ventricular arrhythmic events. We found that overall, the median beats of VT before termination was 19. However, the fast VT that was induced (mean CL of 230 ms) in the current study necessitated early intervention in the form of ATP, direct current cardioversion, or both. It has previously been shown that the sympathetic response to VT is dramatic in the first 10 s, leading to profound hemodynamic decompensation and directly proportional to the rate of the tachycardia.[18] Hence, definitions for sustained inducible VT at EPS should be revised to include these short durations of rapid VT. We propose a new definition for the duration of inducible VT at early EPS after acute MI. Sustained VT should be defined as >8 beats and >2 s. Nonsustained VT should be defined as <8 beats and <2 s duration.

Reperfusion times have substantially improved the prognosis of STEMI patients, with benefits of reperfusion persisting up to 12 hours after symptom onset, but the greatest benefit is within the first 90 minutes.[19–22] International guidelines have implemented a 90-minute door-to-balloon time to reflect this, and multiple studies have shown that shorter door-to-balloon times lead to smaller infarct sizes.[23–26] Magnetic resonance imaging studies of infarcted

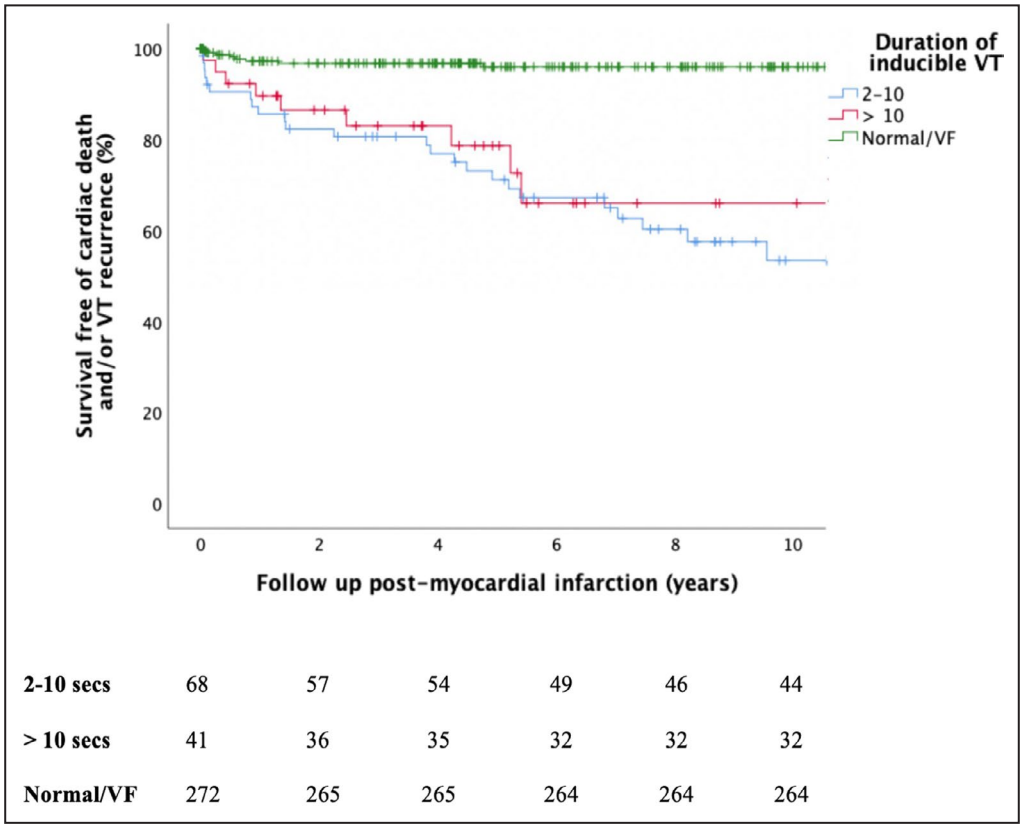

Figure 1. Cardiac mortality and ventricular tachycardia (VT) recurrence (*P*=0.001).
VF indicates ventricular fibrillation.

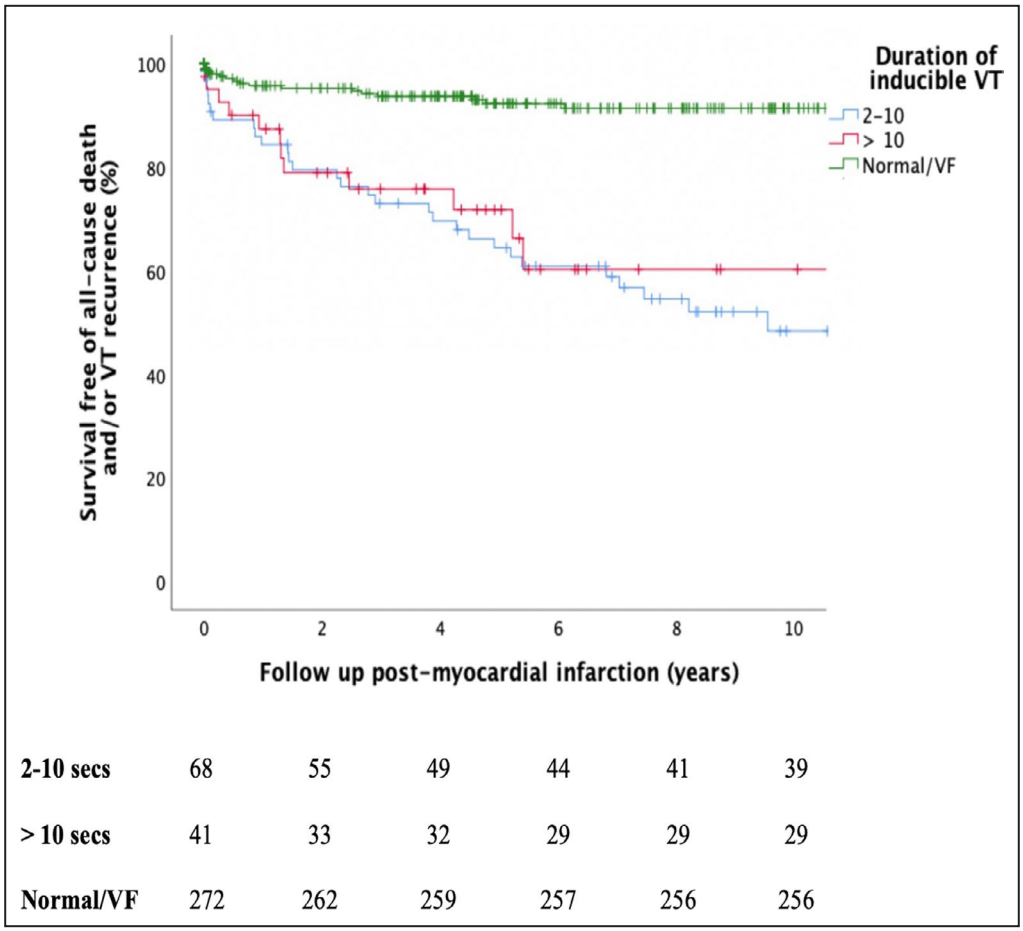

Figure 2. All-cause mortality and ventricular tachycardia (VT) recurrence (*P*=0.001).
VF indicates ventricular fibrillation.

hearts have shown that delayed or failed reperfusion results in increased infarct size and greater degrees of microvascular occlusion that can increase VT inducibility.[27,28] It has been well recognized that reentry through a stable circuit involving infarct scar tissue is the most likely mechanism of sustained monomorphic VT after infarction.[29] Presumably, early reperfusion results in small areas of surviving myocardium at the infarct border zone, allowing for smaller reentry circuits capable of sustaining faster VT. Reentry circuits that are too small may not be capable of maintaining VT, as the depolarizing wave front encounters refractory myocardium. This may provide a rationale for faster VT and less arrhythmogenesis in the context of early reperfusion.[30,31] EPS has been predictive of arrhythmic events (odds ratio, 2.97; 95% CI, 1.44–6.12) but not total mortality (odds ratio, 1.16; 95% CI, 0.64–2.11).[32] These findings are consistent in our study.

In 4 studies from a recent meta-analysis, EPS performed early after MI testing for ventricular arrhythmia inducibility showed a high predictive power for the subsequent arrhythmic events (odds ratio, 7.85).[32] Kumar et al[10] showed that a delay in reperfusion led to a 6-fold increase in inducible VT at EPS early after MI and a 3-fold increase in spontaneous VT at 2-year follow-up. Nalliah et al[33] have previously shown that inducible VT was faster in primary prevention patients receiving early reperfusion for acute MI. They showed that patients who had early reperfusion treatment (within 12 hours of symptom onset) had faster inducible VT compared with patients who did not (231±43 ms versus 252±56 ms; *P*=0.016). Patients who received late reperfusion were also 3 times more likely to experience appropriate defibrillator activation or sudden cardiac death compared with patients who received early reperfusion. Piers et al[7] similarly demonstrated the occurrence of faster inducible VT in secondary prevention patients with effective early reperfusion after MI. They classified early reperfusion treatment as <9 hours from symptom onset. Patients who underwent primary PCI were compared with nonreperfused patients and had significantly faster CLs (238±40 ms versus 287±63 ms; *P*<0.001). Fast VT (<250 ms) was also more prevalent in the early reperfusion group. Chong et al[34] showed a nonsignificant difference for the mean CL of inducible

VT after STEMI for those who received primary PCI or thrombolysis as their initial treatment (246+48 ms versus 261+62 ms; *P*=0.65).

Previous studies have shown that it is actually the rate of VT that appears to be the main factor that determines hemodynamic instability rather than baseline left ventricular function.[18,35,36] Hemodynamic instability during VT has been proposed to be caused by 2 main mechanisms: uncoordinated ventricular contraction and reduced diastolic filling. Decreased coordination of contraction and relaxation is critical in patients with depressed left ventricular function. Decreased systolic left ventricular function during VT is dependent on left ventricular filling, which is further compromised by impaired diastolic left ventricular relaxation resulting from abnormal contraction patterns after MI.[37–39] Hemodynamic instability is compounded by a profound rapid initial phase, which comes into play during the first 30 s of VT, which is mediated by arterial baroreflexes.[18] The induction of fast VT has become more relevant in the contemporary era of early and more effective reperfusion with primary PCI and, as reinforced in our study, it now can be seen to make up most of inducible VT early after MI. Our study also reinforces the utility of ATP in termination of fast VT. These results are consistent with previous studies that have shown similar results in both early EPS after MI[9] and ICD trials.[40]

Several articles have confirmed the utility of the inducibility of VT in predicting future arrhythmic events. Zaman et al[9] have shown that fast VT (CL 200–230 ms) confers a similar risk of arrhythmia or death as standard VT (CL >230 ms) and a significantly higher risk compared with patients with a negative EPS. Furthermore, they have shown that this applies to inducible VT with a second PVS if the first was negative[11] and 4 extrastimuli compared with 3.[8] Conversely, patients who have a negative EPS, being no arrhythmia induced or inducible ventricular flutter/VF, have been shown to have good long-term prognosis without the insertion of an ICD. Zaman et al[6] showed that patients with LVEF <30% or <35% with evidence of heart failure, who had no inducible VT at early EPS, had a similar 3-year survival free of death or arrhythmia compared with patients with LVEF >40% (93% versus 91%; *P*=0.738), demonstrating the excellent negative predictive value of PVS early after MI. Similarly, Kumar et al[5] showed that patients with a negative EPS without a defibrillator had a significantly lower risk for the primary end point, defined as sudden death or spontaneous ventricular arrhythmia, than patients with inducible VT with a defibrillator (adjusted hazard ratio, 0.34; *P*=0.011). The risk of sudden cardiac death in the negative electrophysiology cohort from this study at 2 years was only 3%. Confirmation of an EPS-guided strategy for primary prevention of sudden cardiac death requires a large, multicenter, randomized, controlled trial such as the current PROTECT-ICD trial, which has a VT induction protocol similar to our study.[41]

Limitations of this study include the lack of randomization and small sample size. However, if we were to run a randomized controlled trial to detect even a 5% difference in the composite end point of VT recurrence or cardiac mortality, we would require >1000 patients in each group. The routine use of EPS early after MI to guide ICD implantation is part of a study protocol, and is limited by its invasiveness, adverse effects, and costs. Nevertheless, these drawbacks may be outweighed by an improvement in ICD implantation appropriateness, which is currently under investigation in a randomized trial.[41] It is also not clear whether the same definitions would apply for inducible VT months or years after MI. It is a limitation of the article that there is a possibility that more events have been reported in the patients with an AICD compared with those without a device. We also accept that it is possible that electrophysiologists' initiated cardioversion when rapid VT was initiated might have contributed to some of the short durations of inducible VT. Hence, the duration of the induced VT might be partly operator dependent.

CONCLUSIONS

This study is the first to show that inducible VT at early postinfarct EPS that lasted 2 to 10 s had similar predictive power as inducible VT of >10 s, in regards to VT recurrence on long-term follow-up, which was significantly different to those without inducible VT. Short duration of inducible VT might have been interrupted because of electrophysiologists' initiated cardioversion. Median durations of inducible VT of 4 and 20 s had similar prognostic value for the combined end point of cardiac mortality or VT recurrence on long-term follow-up.

ARTICLE INFORMATION

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Affiliations

From the Department of Cardiology, Westmead Hospital, Sydney, Australia (T.D., A.N., P.K.); University of Sydney, Sydney, Australia (T.D., P.K.); Monash University, Melbourne, Australia (S.Z.); and Monash Cardiovascular Research Centre, Monash Heart, Melbourne, Australia (S.Z.).

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Disclosures

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